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Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial

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Summary

Background Diabetic retinopathy remains a leading cause of visual loss in people of working age. We examined whether candesartan treatment could slow the progression and, secondly, induce regression of retinopathy in people with type 2 diabetes.

Methods We did a randomised, double-blind, parallel-group, placebo-controlled trial in 309 centres worldwide. We recruited normoalbuminuric, normotensive, or treated hypertensive people with type 2 diabetes with mild to moderately severe retinopathy and assigned them to candesartan 16 mg once a day or placebo. After a month, the dose was doubled to 32 mg once per day. Investigators and patients were unaware of the treatment allocation status. Progression of retinopathy was the primary endpoint, and regression was a secondary endpoint. Analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00252694.

Findings 1905 participants (aged 37–75 years) were randomised to candesartan (n=951) or placebo (n=954). 161 (17%) patients in the candesartan group and 182 (19%) in the placebo group had progression of retinopathy by three steps or more on the Early Treatment Diabetic Retinopathy Study scale. The risk of progression of retinopathy was non-significantly reduced by 13% in patients on candesartan compared with those on placebo (hazard ratio [HR] 0·87, 95% CI 0·70–1·08, p=0·20). Regression on active treatment was increased by 34% (1·34, 1·08–1·68, p=0·009). HRs were not attenuated by adjustment for baseline risk factors or changes in blood pressure during the trial. An overall change towards less severe retinopathy by the end of the trial was observed in the candesartan group (odds 1·17, 95% CI 1·05–1·30, p=0·003). Adverse events did not differ between the treatment groups.

Interpretation Treatment with candesartan in type 2 diabetic patients with mild to moderate retinopathy might induce improvement of retinopathy.

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Introduction

Diabetic eye disease, including retinopathy with macular oedema, remains the leading cause of blindness in people of working age.[1,2] At diagnosis, nearly 40% of people with type 2 diabetes already have some degree of retinopathy; another 22% will develop it over 6 years.[3]

Strict glycaemic control and control of blood pressure in those with hypertension substantially reduce the progression of diabetic eye disease.[4–6] Lowering blood pressure, can also be of benefit, even in normotensive patients,[6] although retinopathy has not been tested as a primary outcome. Optimal control of blood glucose and blood pressure, however, is not achievable in all patients with type 2 diabetes[7,8] and, even when obtained, is not always effective.[9] Laser photocoagulation can reduce the risk of blindness from proliferative retinopathy,[10] but is less effective for treatment of diffuse macular oedema,[11] and has side-effects.[10]

The specific role of blockade of the renin–angiotensin system has not been studied in retinopathy in type 2 diabetes, whereas it has been shown to reduce risks for nephropathy and cardiovascular disease.[12–17] Angiotensin receptor blockers are now recommended for people with type 2 diabetes with microalbuminuria or macroalbuminuria,[18] and might prevent development of microalbuminuria in hypertensive patients with type 2 diabetes.[19] We designed three separate randomised, double-blind, placebo-controlled clinical trials to assess whether the angiotensin receptor blocker candesartan could reduce the incidence of retinopathy in type 1 diabetes (DIabetic REtinopathy Candesartan Trials [DIRECT]-Prevent 1); progression of retinopathy in type 1 diabetes (DIRECT-Protect 1); and progression of retinopathy in type 2 diabetes (DIRECT-Protect 2). In this paper, we report the findings of the third trial.

Methods

Participants

The study design and baseline data have previously been described in detail.[20,21] We screened men and women who were aged 37–75 years and had known type 2 diabetes for between 1 and 20 years in 309 centres worldwide. Inclusion criteria were age at onset of 36 years or older, and no need for continuous insulin treatment within a

	Severity	Definition
10	DR absent	All DR features absent
20	MA only	MA(s) only, other lesions absent
35	Mild NPDR	MA plus retinal haemorrhage(s), HEs, or CWSs
43	Moderate NPDR	Lesions as above and either extensive or severe HMAs or IRMAs present
47	Moderately severe NPDR	Lesions of level 35 and either extensive or severe HMAs with IRMAs or venous beading
53	Severe NPDR	Extensive and severe HMAs, IRMAs or, venous beading, or both
61, 65, 71, 75, 81	PDR	NVD or NVE, or both, without or with complications

Clinically significant macular oedema (CSME) was graded according to the criteria in the DIRECT Programme—ie, 0=no evidence of CSME; 1=questionable presence of CSME; 2=non-CSME but macular thickening; 3=definite CSME due to retinal thickening of at least one disc area, any part of which lies within one disc diameter from the fovea; and 4=definite CSME due to thickening or hard exudates less than 500 µm from the fovea. CWSs=cotton-wool spots. DR=diabetic retinopathy. HEs=hard exudates. HMAs=haemorrhages and microaneurysm. IRMAs=intraretinal microvascular abnormalities. MA=microaneurysms. NPDR=non-proliferative diabetic retinopathy. NVD=new vessels on the optic disc. NVE=new vessels elsewhere. PDR=proliferative diabetic retinopathy.

Table 1: **Severity and lesions defining level on the Early Treatment Diabetic Retinopathy Study scale used for the DIabetic REtinopathy Candesartan Trials (DIRECT) Programme**

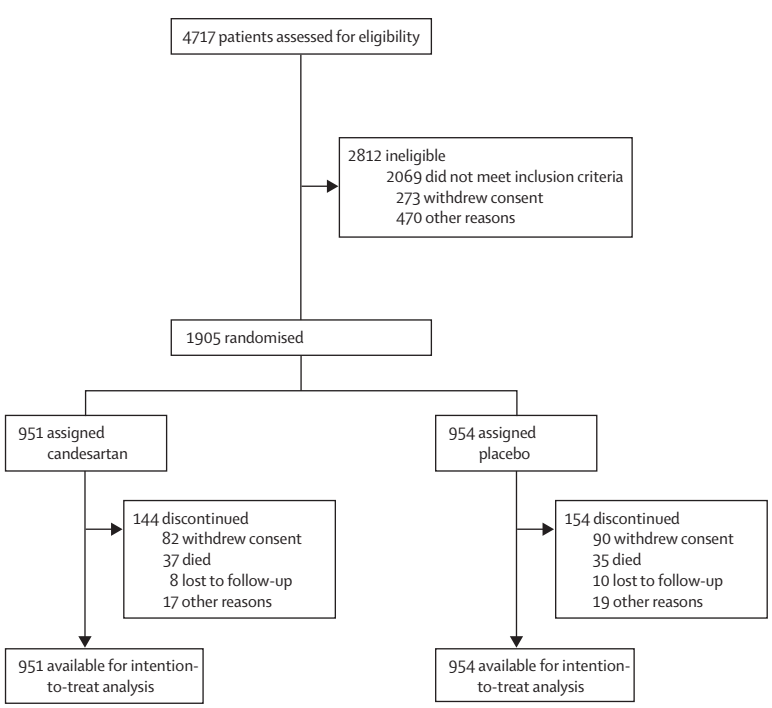

Figure 1: **Trial profile**

year of diagnosis. We excluded patients who had eye conditions that precluded capture of gradable retinal photographs (ie, dense cataracts and angle-closure glaucoma); those with clinically significant macular oedema or proliferative retinopathy, and those who had stenotic valvular heart disease, recent stroke, or myocardial infarction. We also excluded pregnant and lactating women, and patients with renal impairment (women with serum creatinine >110 µmol/L and men with serum creatinine >130 µmol/L).

We obtained two overnight urine samples, which were analysed for albumin at a central laboratory, using nephelometry. Patients were excluded if results showed that urinary albumin excretion rate in at least one of the two samples was not less than 20 µg/min, indicating normoalbuminuria. If patients were not on antihypertensive treatment, they had to have systolic/diastolic blood pressure of less than or equal to 130/85 mm Hg; or if they were on antihypertensive treatment, a blood pressure of less than or equal to 160/90 mm Hg. Patients who were taking renin–angiotensin system inhibitors were excluded. Patients also had to have mild to moderately severe non-proliferative diabetic retinopathy, assessed by a score of 20/10 or more and 47/47 or less on the severity scale used in the Early Treatment Diabetic Retinopathy Study (ETDRS; table 1).[22,23]

Conduct of the study was overseen by a steering committee. The programme was approved by national and local ethics committees and regulatory bodies at all participating centres. An independent safety committee regularly reviewed safety data. All patients provided written informed consent.

Procedures

Random assignment was done centrally, using an interactive voice-response system. Both investigators and participants were unaware of the treatment allocation of each participant. Participants were randomly assigned to receive candesartan 16 mg once a day or matching placebo. After a month, this dose was doubled to 32 mg once a day of either treatment. An adjustment to 16 mg once a day or 8 mg once a day could be made at any time during the study. We assessed blood pressure and adverse events every 6 months, and did all other tests once a year and at the final visit. All participants were followed up for at least 4 years.

We took retinal photographs at 6 months, 1 year, and every year thereafter. Seven-field stereo photographs of both eyes were taken according to the ETDRS protocol.[22,23] Two grading teams of independent observers, each consisting of a primary and a secondary grader, were assigned to each patient for the duration of the study at the Retinopathy Grading Centre, Imperial College London, UK. Graders, who were unaware of treatment allocation, assessed all photographs for retinopathy. The ETDRS scale has 11 assignable levels of increasing severity for retinopathy (table 1). Each eye was graded separately. The Academic Coordinating Centre, Imperial College London, UK undertook regular quality assurance cycle procedures to test reliability and repeatability. Each grading team was asked to assess a master set of 52 fundus photograph sets (104 eyes), across the range of

retinopathy severity, without knowing whether it was part of the quality assurance cycle procedure or the study. Each team assessed the master set six times throughout the trial. Unweighted interteam kappa statistics between teams were 0·73, 0·63, 0·67, 0·67, 0·63, and 0·68 for the six cycles, and agreement within teams (comparing current with baseline or previous cycle) varied from 0·64 to 0·79 (median 0·74).

Other standardised procedures included automated measurement of blood pressure (Omron M4, Omron Healthcare, Kyoto, Japan) in the seated position after 5 min of rest. Three measurements were taken, and the mean of the last two measurements was used in the analysis. Blood samples were taken for measurements of HbA_{1c}, serum total cholesterol, HDL cholesterol, and creatinine. All assays were done at a central laboratory.

The primary endpoint was progression of retinopathy, defined as an increase in three or more ETDRS levels (ie, at least two steps in one eye and one step in the other, or at least three steps in one eye with the other remaining unchanged).[20] An additional prespecified outcome measure was overall change in retinopathy levels from baseline to final visit, by treatment group.

Secondary endpoints were regression of retinopathy (defined as a reduction of at least three or more steps on the ETDRS scale from baseline to any follow-up visit, or two or more steps sustained at two consecutive follow-up visits); and development of proliferative diabetic retinopathy, clinically significant macular oedema, or both. Clinically significant macular oedema was diagnosed as retinal thickening of one or more disc area (any part of which lies less than a disc diameter from the fovea) or hard exudates less than 500 μm from the fovea.

Statistical methods

We planned to include 1700 patients with a follow-up of at least 3 years. The calculated power to detect a 27% reduction due to treatment in three-step or more progression of retinopathy was estimated to be approximately 80% at 5% significance level.[21] The study was extended by 1 year because the event rate was lower than expected. We analysed all patients according to intention to treat, and calculated all p values without adjustment due to the prespecified hierarchical testing strategy.

The primary outcome was the time from baseline to the first occurrence of an increase of at least three steps on the ETDRS scale. The exact time of an event was not known more precisely than the time between two fundus photographs. Therefore, we used the non-parametric generalised log-rank test for the primary analysis, to compare the distributions of the time to an event for placebo and candesartan.[24] Non-parametric maximum likelihood estimators for censored data enabled these distributions to be shown on a graph.[25] To estimate the treatment effect, we calculated 95% CIs for the hazard ratio (HR) using a generalisation of a Cox-regression model.[26] If a photograph for only one eye was missing at a visit, we used the photograph from the previous visit.

We used a Wilcoxon-Mann-Whitney test to assess whether the distribution of the change in severity of retinopathy from baseline differed by treatment.

	Candesartan (N=951)	Placebo (N=954)
Men	466 (49%)	482 (51%)
Age (years)	56·9 (7·6)	56·8 (7·9)
Caucasian	916 (96·3%)	914 (95·8%)
Retinopathy level in worst eye (ETDRS scale)		
10	4 (0%)	1 (0%)
20	271 (28%)	273 (29%)
35	532 (56%)	502 (53%)
>35	144 (15%)	178 (19%)
Duration of diabetes (years)	8·8 (4·9)	8·7 (4·8)
Treatment for diabetes		
No pharmacological treatment	22 (2%)	20 (2%)
Insulin only	159 (17%)	170 (18%)
Oral hypoglycaemic agent only	592 (62%)	581 (61%)
Insulin and oral hypoglycaemic agent	178 (19%)	183 (19%)
HbA_{1c} (%)	8·2 (1·6)	8·2 (1·6)
Treated for hypertension	588 (62%)	592 (62%)
Systolic blood pressure (mm Hg) normotensive	123 (8·7)	123 (9·0)
Treated hypertensive	139 (12·7)	139 (12·0)
Diastolic blood pressure (mm Hg) normotensive	75 (6·4)	76 (6·5)
Treated hypertensive	79 (6·9)	80 (7·1)
Body-mass index (kg/m²)	29·4 (4·6)	29·4 (4·8)
Total serum cholesterol (mmol/L)	5·3 (1·1)	5·3 (1·1)
Serum non-HDL lipoprotein cholesterol (mmol/L)	3·9 (1·0)	3·9 (1·1)
Serum creatinine (μmol/L)	90·3 (15·5)	90·1 (15·2)
Urinary albumin excretion rate (μg/min)	5·5 (3·5, 8·5)	5·5 (3·5, 8·5)
Smoking (ex-smoker or current)	253 (27%)	259 (27%)
Cardiovascular disease		
Previous myocardial infarction	49 (5%)	50 (5%)
Previous stroke	16 (2%)	10 (1%)

Data are mean (SD), number (%), or median (IQR). OHA=oral hypoglycaemic agents. ETDRS=Early Treatment Diabetic Retinopathy Study.

Table 2: **Baseline characteristics**

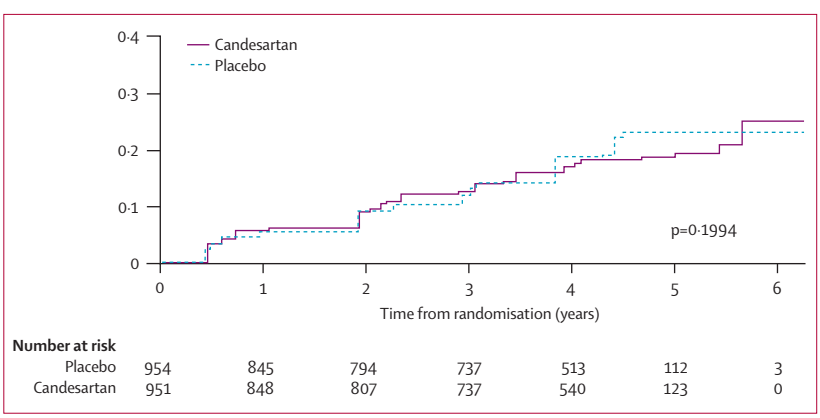

Figure 2: **Cumulative proportion of patients with progression of retinopathy by treatment allocation**

	Hazard ratio (95% CI)	p value
Unadjusted	0·87 (0·70–1·08)	0·199
Adjusted*	0·86 (0·69–1·06)	0·156
Adjusted†	0·89 (0·72–1·10)	0·288

*Adjusted for the following baseline characteristics: retinopathy level, duration of diabetes, urinary albumin excretion rate, HbA_{1c}, antihypertensive treatment, and systolic blood pressure. †Adjusted for the following baseline characteristics: retinopathy level, duration of diabetes, urinary albumin excretion rate, HbA_{1c}, antihypertensive treatment, and systolic blood pressure as a time-dependent covariate.

Table 3: **Estimated hazard ratios for candesartan versus placebo for time to three-step progression of retinopathy (intention-to-treat population)**

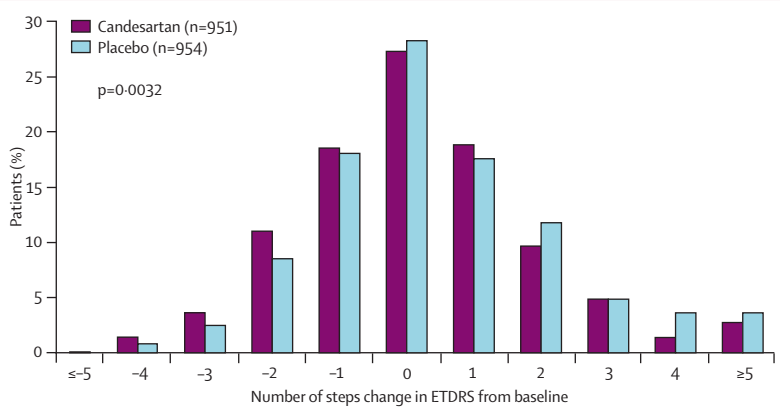

Figure 3: **Distribution of changes in ETDRS level during study, by treatment group**

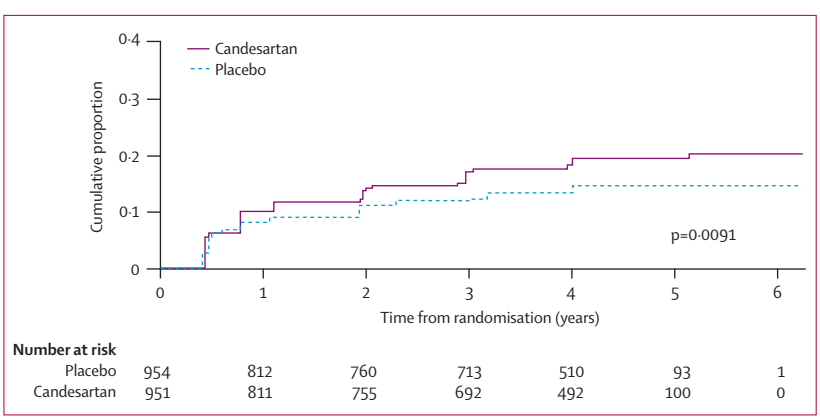

Figure 4: **Cumulative proportion of patients with regression of retinopathy, by treatment group**

We calculated the corresponding odds between treatments.[27]

The trial is registered with ClinicalTrials.gov, number NCT00252694.

Role of funding source

The sponsors of the study did the statistical analysis, with validation by an independent statistician. Data were gathered by investigators, and data management was done by ICON on behalf of the sponsors. The study protocol was designed by members of the steering committee. The authors had full access to all data, and were free to interpret the data, and draw conclusions. The corresponding author had full access to all data, and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Randomisation commenced in August, 2001, and was completed in February, 2004. The last patient was evaluated in March, 2008. Median follow-up was 4·7 years. Table 2 shows that baseline clinical characteristics did not differ between placebo and candesartan groups.

688 (36%) of 1905 patients were receiving insulin treatment at randomisation, and 1015 (53%) during the study, with no difference between treatment groups. Of 1015 receiving insulin during the study, 501 patients were treated with candesartan and 514 were treated with placebo (p=0·60). HbA_{1c} concentrations were stable over time, with no difference in mean values between the treatment groups (p=0·48).

At baseline, 1180 (62%) of 1905 patients were treated for hypertension with medication other than inhibitors of the renin–angiotensin system, and with an almost equal distribution of β blockers, diuretics, and calcium-antagonists. During the study, 685 (72%) of 951 patients in the candesartan group and 731 (77%) of 954 patients in the placebo group were on any antihypertensive treatment (p=0·026). 196 (21%) in the candesartan group and 271 (28%) in the placebo group were treated with renin–angiotensin system inhibitors (p<0·0001). 818 (86%) patients were taking the maximum candesartan dose of 32 mg at the end of the study.

The mean change in systolic/diastolic blood pressure was 4·3/2·5 mm Hg greater in the candesartan group than in the placebo group at the final visit for patients who were receiving antihypertensive treatment at baseline (p<0·0001 for both). For those not on such treatment, the difference in change was 2·9/1·3 mm Hg (p=0·0003/p=0·0045). The reduction in blood pressure was observed within 2 months after random assignment and persisted for the duration of the trial.

161 (17%) of 951 patients in the candesartan group and 182 (19%) of 954 in the placebo group had progression of retinopathy by three steps or more on the ETDRS scale—the primary outcome (HR 0·87, 95% CI 0 ·70–1·08, p=0·20) (figure 2; table 3). Adjustment for baseline covariates, with systolic blood pressure and HbA_{1c} as time-dependent variables did not change the HR. Separate assessment of these variables showed that HbA_{1c} and retinopathy at baseline affected the progression of retinopathy (data not shown). Figure 3 shows that participants in the candesartan group were more likely to have an overall improvement in retinopathy by the end of the trial than those in the placebo group (odds 1·17, 95% CI 1·05–1·30, p=0·003).

180 (19%) of 951 participants in the candesartan group and 136 (14%) of 954 controls had regression of retinopathy,

which showed that candesartan was associated with a 34% increase in the relative chance of regression (p=0·009) (figure 4; table 4). This beneficial effect was not altered by baseline covariates or change in systolic blood pressure during the study (table 4). Analysis of the relation between retinopathy at baseline and the chance of regression (figure 5) showed that the treatment effect was significant in patients with mild retinopathy (level 35), but not in those with moderate to moderately severe retinopathy (p=0·064 for interaction). From these data, 21 patients would need to be treated with candesartan for 4·7 years to obtain regression of retinopathy in one patient.

192 (20%) of 951 patients in the candesartan group and 193 (20%) of 954 controls had proliferative diabetic retinopathy, clinically significant macular oedema, or both (HR 0·971, p=0·773).

Adverse events did not differ in the candesartan and placebo groups (table 5). The safety population was defined as all patients who received at least one dose of randomised investigational product and for whom any post-dose data were available. Three patients were excluded from the safety population as randomised investigational products were not dispensed (two in the candesartan group and one in the placebo group, respectively). The four most common adverse events were hypertension, headache, influenza, and pain in extremities. Permanent discontinuation and mortality proportions did not differ by treatment allocation.

Discussion

We found that treatment with the angiotensin receptor blocker candesartan during a 4 year trial resulted in a non-significant reduction in progression of retinopathy, the primary endpoint. At the end of the trial, those participants on candesartan had a significantly favourable change in retinopathy levels, a prespecified outcome measure, compared with placebo. We also showed a significant regression of retinopathy, the main secondary endpoint, in the candesartan-treated group compared with those on placebo.

Candesartan did not affect the incidence of proliferative diabetic retinopathy or clinically significant macular oedema, or both. About a fifth of participants had these manifestations; this proportion is higher than might be seen clinically, and indicates our use of a more sensitive research purpose grading system.

The treatment curves for progression of retinopathy in patients in this study only began to diverge after 4 years of follow-up. In the UK Prospective Diabetes Study (UKPDS),[28] no treatment effect on progression was observed at 1·5 years in those with retinopathy at baseline. A significant effect was only recorded at 4·5 years.[28] In the ABCD trial,[6] blood pressure at baseline was similar to values recorded in our study, but a mean treatment difference of 11 mm Hg systolic pressure was achieved in the group given intensive treatment compared with those given moderate treatment over 5·3 years

	Hazard ratio (95% CI)	p value
Unadjusted	1·34 (1·08–1·68)	0·009
Adjusted*	1·38 (1·11–1·73)	0·004
Adjusted†	1·33 (1·06–1·67)	0·015

*Adjusted for the following baseline characteristics: retinopathy level, duration of diabetes, urinary albumin excretion rate, HbA_{1c}, antihypertensive treatment, and systolic blood pressure. †Adjusted for the following baseline characteristics: retinopathy level, duration of diabetes, urinary albumin excretion rate, HbA_{1c}, antihypertensive treatment, and systolic blood pressure as a time-dependent covariate.

Table 4: **Estimated hazard ratios for candesartan versus placebo for time to regression of retinopathy (intention-to-treat population)**

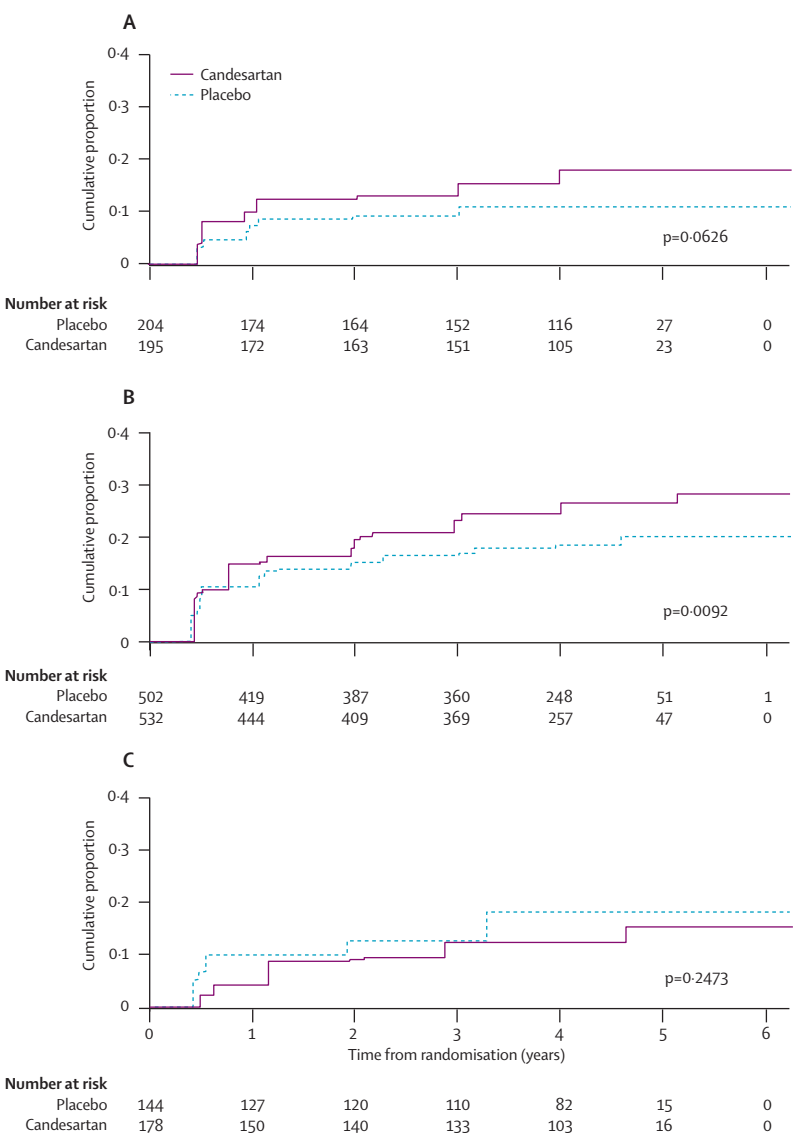

Figure 5: **Cumulative proportion of patients with regression of retinopathy, grouped by retinopathy level at baseline**

(A) Microaneurysms only. (B) Mild non-proliferative diabetic retinopathy. (C) Moderate to moderately severe retinopathy.

	Candesartan (N=949)	Placebo (N=953)
All adverse events	796 (84%)	786 (83%)
Hypertension	124 (13%)	173 (18%)
Headache	79 (8%)	94 (10%)
Influenza	77 (8%)	83 (9%)
Pain in extremities	79 (8%)	79 (8%)
Discontinued study medication because of adverse event	37 (4%)	42 (4%)
Death	37 (4%)	35 (4%)

Data are number of patients (%).

Table 5: **Adverse events for the safety population**

(using either an angiotensin-converting enzyme inhibitor or a calcium-channel blocker). Progression of two steps was also lower in the intensive blood pressure group (34% *vs* 46%)—ie, a 12% absolute reduction.[6] We recorded a 2% (19% *vs* 17%) absolute reduction in progression of retinopathy by three or more steps. Although this absolute reduction was smaller than that reported in the ABCD trial, it is in keeping with the much smaller difference in mean blood pressure associated with candesartan treatment.

However, differences between studies limit such comparisons. Both the UKPDS and the ABCD trials used a two-step change on the ETDRS scale as their retinopathy endpoint; included patients who were hypertensive; and maintained different blood pressure in each treatment group. We enrolled patients who were either normotensive or treated hypertensive, and did not aim to treat blood pressure to a given target, although a small difference in the range of 2–4 mm Hg was seen between the candesartan and placebo groups. Analysis of progression of retinopathy, adjusting for blood pressure at baseline and during the course of the trial, did not materially change HRs. However, small differences between treatment groups in resting blood pressure can allow large treatment differences in diurnal patterns of blood pressure,[29] and we therefore cannot robustly conclude that any beneficial effect of candesartan on retinopathy is independent of its effect on lowering blood pressure.

We showed that candesartan treatment was associated with a 34% increase in regression of retinopathy. In a subgroup analysis, patients with mild retinopathy (level 35) regressed significantly, whereas the effect on more severe retinopathy was less evident. The robustness of our criteria for regression (either a three-step decrease in severity of retinopathy on the ETDRS scale from baseline at one time point, or a two-step decrease sustained on two consecutive visits), along with its independence of potential confounders, suggest that this treatment effect on regression is a genuine finding. Candesartan has been shown to induce regression of end-organ damage at other sites, including left-ventricular hypertrophy and intima-media thickness,[30,31] and its effect on retinopathy might represent another facet of its activity. This is of particular interest in light of recent reports that diabetic retinopathy is associated with increased cardiovascular mortality,[32–34] reduced coronary reactivity,[35] and poorer prognosis of coronary revascularisation procedures.[36,37] Diabetic retinopathy might thus be a readily visible marker of diffuse endothelial damage at microvascular and macrovascular levels; however, no clinical trial data show that agents able to induce regression of retinopathy have similar beneficial effects on other cardiovascular endpoints.

Our study design did not enable us to identify the mechanism by which blocking the renin–angiotensin system could affect regression of diabetic retinopathy. As discussed, this could simply be due to lowering of blood pressure. However, a local renin–angiotensin system operates in the eye,[38,39] and is upregulated in active retinopathy.[40,41] Angiotensin II might directly, or by upregulation of growth factors such as VEGF, induce exudation from the retinal capillaries,[42] causing appearance of haemorrhages, hard exudates, and thickening of the retina in the macular area.[43] We speculate that the regression of retinopathy associated with candesartan treatment could in part be due to a reduction of the exudative process occurring at an early stage. At a more advanced stage, at which ischaemic changes are predominant, retinopathy might have reached a so-called point of no return, indicating that treatment with an angiotensin receptor blocker is most beneficial at relatively early stages of the disease. This suggestion is supported by the lack of effectiveness of losartan on macular oedema, in a short, small pilot study.[44]

Experimental studies have indicated that candesartan has a dose-dependent organ protective effect.[45,46] We chose a relatively high dose, aiming at 32 mg per day. Rates of adverse event rates did not differ in the treatment groups, which supports the safety of the drug at the administered dose.[47,48]

Treatment with the angiotensin receptor blocker candesartan over a 4 year trial reduced the primary endpoint of progression of retinopathy by 13% versus placebo in normoalbuminuric, normotensive, or controlled hypertensive patients with type 2 diabetes, although this reduction was not significant. Patients given candesartan were a third more likely to experience regression of retinopathy (a secondary endpoint) and more likely to end the trial with a more favourable retinopathy status (a prespecified outcome measure), due both to greater regression and lesser progression. These results suggest that treatment with candesartan in type 2 diabetic patients with mild to moderate retinopathy could induce improvement of retinopathy.

Contributors

Each author contributed to the design, conduct, analysis, and interpretation of the DIRECT Programme, and specifically, to the interpretation of findings of the analyses presented here. AKS drafted the manuscript, and other authors contributed to the writing. All authors have seen and approved the final manuscript.

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Conflict of interest statement

All authors have received travel grants and consultancy fees for attending committee meetings; AKS, MP, and RB received fees as national coordinators, and AKS, JF, HHP, RB, and NC have received honoraria for scientific presentations from AstraZeneca and Takeda.

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